# A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease

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Editorial, page 1198

Supplemental data at www.neurology.org

Supplemental Data

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## ABSTRACT

**Objective:** To evaluate the efficacy and safety of a selective serotonin reuptake inhibitor (SSRI) and a serotonin and norepinephrine reuptake inhibitor (SNRI) in the treatment of depression in Parkinson disease (PD).

**Methods:** A total of 115 subjects with PD were enrolled at 20 sites. Subjects were randomized to receive an SSRI (paroxetine; n = 42), an SNRI (venlafaxine extended release [XR]; n = 34), or placebo (n = 39). Subjects met *DSM-IV* criteria for a depressive disorder, or operationally defined subsyndromal depression, and scored >12 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D). Subjects were followed for 12 weeks (6-week dosage adjustment, 6-week maintenance). Maximum daily dosages were 40 mg for paroxetine and 225 mg for venlafaxine XR. The primary outcome measure was change in the HAM-D score from baseline to week 12.

**Results:** Treatment effects (relative to placebo), expressed as mean 12-week reductions in HAM-D score, were 6.2 points (97.5% confidence interval [CI] 2.2 to 10.3, $p = 0.0007$) in the paroxetine group and 4.2 points (97.5% CI 0.1 to 8.4, $p = 0.02$) in the venlafaxine XR group. No treatment effects were seen on motor function.

**Conclusions:** Both paroxetine and venlafaxine XR significantly improved depression in subjects with PD. Both medications were generally safe and well tolerated and did not worsen motor function.

**Classification of Evidence:** This study provides Class I evidence that paroxetine and venlafaxine XR are effective in treating depression in patients with PD. ***Neurology*® 2012;78:1229–1236**

## GLOSSARY

**BDI-II** = Beck Depression Inventory II; **CGI** = Clinical Global Impression Scale; **CI** = confidence interval; **CTCC** = Clinical Trials Coordination Center; **dPD** = depression in Parkinson disease; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition; **GDS** = Geriatric Depression Scale; **HAM-D** = Hamilton Rating Scale for Depression; **MADRS** = Montgomery-Åsberg Depression Rating Scale; **PD** = Parkinson disease; **SAD-PD** = Study of Antidepressants in Parkinson Disease; **SF** = Short Form; **SNRI** = serotonin and norepinephrine reuptake inhibitor; **SSRI** = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant; **UPDRS** = Unified Parkinson's Disease Rating Scale; **XR** = extended release.

Depression in Parkinson disease (PD) (dPD) is associated with functional impairment[1] and reduced quality of life[2–4] but the optimal approach to treatment remains uncertain.

Tricyclic antidepressants (TCAs), which inhibit the reuptake of norepinephrine and serotonin, are efficacious in the treatment of dPD[5,6] but are associated with cardiac, autonomic, and anticholinergic side effects.[7–9]

Selective serotonin reuptake inhibitors (SSRIs) have demonstrated similar efficacy and better tolerability when compared to traditional TCAs in depressed patients without PD[10–15] but

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*Study funding:* Supported by NIH/NINDS R01 NS046487 and the General Clinical Research Center at Johns Hopkins University School of Medicine (National Center for Research Resources/NIH M01-RR00052). Wyeth Pharmaceuticals provided venlafaxine XR and matching placebo. Glaxo-Smith Kline provided paroxetine.

*Disclosure:* Author disclosures are provided at the end of the article.

have been reported to worsen parkinsonian motor features.[16–19] There have been 2 modestly sized, single site, placebo-controlled clinical trials of SSRIs in dPD. A study by Menza et al.[5] suggested that nortriptyline, but not paroxetine, was significantly more effective than placebo. Devos et al.[6] concluded that desipramine and citalopram were more effective than placebo; however, desipramine was not as well tolerated. PD motor function did not appear to be affected in either study.

Serotonin and norepinephrine reuptake inhibitors (SNRIs), like TCAs, act on both neurotransmitter systems but are generally better tolerated. In broader patient populations SNRIs have been shown to be at least as efficacious as SSRIs[20–22] but there have been no controlled trials of SNRIs in dPD.

We present the results of a multicenter randomized, double-blind, placebo-controlled clinical trial of an SSRI, paroxetine, and an SNRI, venlafaxine extended release (XR), in dPD. We hypothesized that both medications would reduce depressive symptoms. We also hypothesized that these medications would be safe and well-tolerated and, in particular, would not worsen PD motor function.

## METHODS

**Standard protocol approvals, registrations, and patient consents.** The study was approved by the institutional review board at each participating institution. Participants provided written informed consent for all procedures after demonstrating capacity to do so.[23] The study is registered with clinicaltrials.gov (trial registration: http://clinicaltrials.gov/ct2/show/NCT00086190).

**Participants.** The Study of Antidepressants in PD (SAD-PD) enrolled 115 participants from 20 centers in the United States, Canada, and Puerto Rico from June 2005 through March 2009. Subjects were recruited from movement disorder clinics. Eligible subjects included men and women ≥30 years of age diagnosed with idiopathic PD, without dementia. Subjects had to meet diagnostic (*DSM-IV*[24]) criteria for a depressive disorder (i.e., major depressive disorder, dysthymic disorder, minor depressive disorder) or operationally defined subsyndromal depression (see online supplemental material on the *Neurology*® Web site at www.neurology.org for details regarding definitions of PD, dementia, and depression). Antidepressant medications other than study drug, antipsychotics, and MAO (including selective B) inhibitors were not permitted. Subjects were excluded if they had had an adequate trial of paroxetine or venlafaxine (see online supplemental material for details and other exclusion criteria).

**Assessment, randomization, and follow-up.** Research participants were initially evaluated during a screening visit at which informed consent was obtained and eligibility criteria and demographic information were verified. The baseline visit occurred within 4 weeks of the screening visit. At this visit, the site coordinator or investigator called the University of Rochester Clinical Trials Coordination Center (CTCC, Rochester, NY) to enroll the participant (see online supplemental material for details of the randomization process and preparation of study medication).

Double-blind treatment lasted 12 weeks and consisted of a 6-week dosage titration period and a 6-week maintenance period. During the dosage titration period (weeks 0–6), participants received 10 mg of paroxetine or 37.5 mg of venlafaxine XR (or matching placebos) each day for the first 2 weeks. The investigator then adjusted the dosage of the experimental medications as necessary and tolerated (up to a maximum daily dosage of 40 mg for paroxetine and 225 mg for venlafaxine XR) to achieve the "optimal dosage" based on a suggested dosage escalation schedule. The investigator was encouraged to increase the dosage until the participant's depression was effectively treated (a suggested criterion was HAM-D score ≤7). The investigator was allowed to decrease or to not escalate the dosage if the participant was experiencing significant adverse events. PD medications were optimized prior to enrollment and every effort was made to maintain stable dosages for the duration of the study.

Participants were evaluated at visits at screening, baseline/randomization, and 2, 4, 6, 8, and 12 weeks after randomization. There was a telephone visit to assess efficacy and tolerability at week 10. Participants who withdrew from the trial were assessed at a final visit.

**Outcome measures.** The primary outcome measure was the change from baseline to week 12 in the 17-item HAM-D,[25] which was administered by the site investigator. The protocol specified that all evaluations should be conducted in the "on" state for patients who experienced motor fluctuations. Details regarding training and reliability assessment for the HAM-D can be found in the online supplemental material.

Secondary outcome measures for antidepressant efficacy included the Montgomery-Åsberg Depression Rating Scale (MADRS),[26] the Beck Depression Inventory II (BDI-II),[27] and the Geriatric Depression Scale (GDS),[28] each administered at all in-person visits. The NIMH Clinical Global Impression Scale (CGI)[29] was also obtained from site investigators and participants at weeks 4, 8, and 12. Prespecified dichotomous HAM-D outcomes were also assessed, including HAM-D ≤7 at week 12 ("remission") and a ≥50% reduction in HAM-D score from baseline to week 12 ("response").

Other outcome measures included the Unified Parkinson's Disease Rating Scale (UPDRS)[30] total and subscale scores[31] to assess PD motor function as well as measures of quality of life, anxiety, psychotic symptoms (a potential side effect of antidepressant medications), sleep, and cognition. A detailed description of these outcome measures is presented in the online supplemental material.

Safety and tolerability outcomes included ability to complete the trial, adverse events, and vital signs. Compliance with study medication was assessed using pill counts at each visit. Participants and investigators were asked to guess the identity of the assigned treatment at week 12 to assess possible compromise of the blind.

**Statistical methods.** Analysis of the primary outcome variable was performed using a repeated-measures analysis of covariance model that included treatment group as the factor of interest with adjustment for site, type of depression (major, nonmajor), and baseline HAM-D score. Week (2, 4, 6, 8, 12, treated as a

categorical variable) and the interaction between treatment group and week were also included in the model. Treatment effects (paroxetine vs placebo, venlafaxine XR vs placebo) were estimated using the adjusted group means obtained from this model, along with corresponding 97.5% confidence intervals (CIs) (Bonferroni-adjusted). Tests of the null hypotheses of zero treatment effects were performed using a 2.5% significance level. The parameters of interest in the repeated-measures analysis of covariance model (treatment effects) were estimated using restricted maximum likelihood, a valid approach for dealing with missing data under the missing at random assumption.[32] All available data from all randomized participants were included in the analysis, in accordance with the intention-to-treat principle. The results using alternative approaches for dealing with missing data (e.g., multiple imputation and last observation carried forward) did not differ substantially from those of the primary analysis and are not reported here. Exploratory analyses of treatment effects in prespecified subgroups of participants were also performed. The methods used for these analyses and the results are presented in the online supplemental material.

Similar analyses were performed for the continuous secondary outcome variables for efficacy as well as vital signs. For categorical outcome variables at week 12 (HAM-D $\leq$7 and $\geq$50% reduction in HAM-D score from baseline), a logistic regression model that included treatment group, type of depression, and baseline HAM-D score as independent variables was used to estimate odds ratios comparing each active treatment group with the placebo group. The logistic regression analyses were performed in 2 ways: 1) using only observed responses and 2) imputing a poor response for those with missing outcomes at week 12. Safety outcomes, medication dosage, compliance, and results of treatment guesses were analyzed descriptively.

A description of the sample size determination and data and safety monitoring for the trial can be found in the online supplemental material.

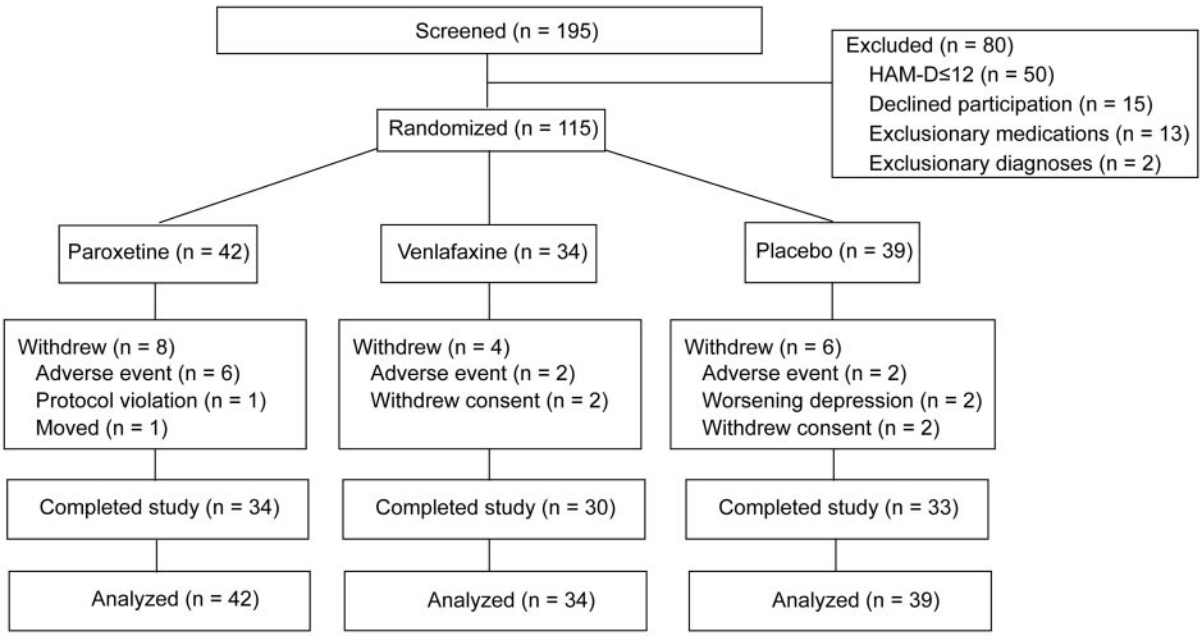
## RESULTS

**Participants.** The flow of participants through the trial is described in figure 1. A total of 115 subjects were randomized to receive paroxetine (n = 42), venlafaxine XR (n = 34), or placebo (n = 39). Eighteen subjects (16%) withdrew participation, 8 (19%) in the paroxetine group, 4 (12%) in the venlafaxine XR group, and 6 (15%) in the placebo group (figure 1). Adverse events led to withdrawal of 6 subjects in the paroxetine group (cardiac arrhythmia; dizziness, nausea, and balance problems; restless legs symptoms; panic attack; sexual dysfunction and lethargy; and insomnia, heartburn, and anxiety), 2 subjects in the venlafaxine group (increased tremor; loss of concentration), and 2 subjects in the placebo group (nausea, palpitations, and stiffness; dizziness and fatigue).

Baseline characteristics of the participants are outlined in table e-1. Participants in the paroxetine group were slightly older on average, more likely to be male, and more likely to be taking levodopa. Participants in the placebo group were less likely to have had education beyond high school and to have major depression. Mean scores on rating scales for depression and PD were comparable among the groups, as were other participant characteristics.

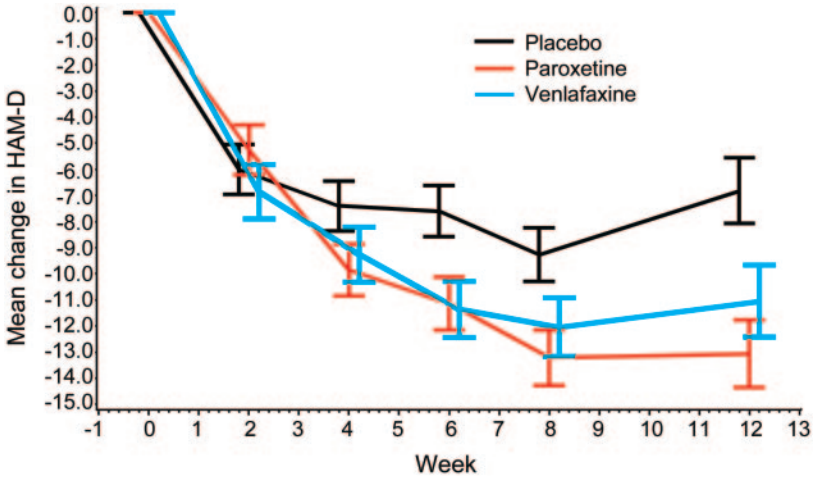
**Efficacy.** All 3 treatment groups demonstrated improvement on the HAM-D at week 12, with mean changes of −13.0 in the paroxetine group, −11.0 in the venlafaxine XR group, and −6.8 in the placebo group (table e-2, figure 2). The effects of paroxetine

**Figure 1** Participant flow




HAM-D = Hamilton Rating Scale for Depression.

**Figure 2** Adjusted mean change in Hamilton Rating Scale for Depression (HAM-D) score over time by treatment group




Mean changes are adjusted for center and the baseline HAM-D score using a repeated-measures analysis of covariance model. Error bars represent 1 SEM.

(−6.2; 97.5% CI −10.3 to −2.2; $p = 0.0007$) and venlafaxine XR (−4.2; 97.5% CI −8.4 to −0.1, $p = 0.02$), relative to placebo, were statistically significant (table e-2). The mean response did not differ significantly between the 2 active treatment groups ($p = 0.28$).

There were no statistically significant differences between medication and placebo groups for dichotomized HAM-D outcomes (table e-3). The percentages of participants who met remission criteria (HAM-D ≤7 at week 12) were 44% (15/34) in the paroxetine group, 37% (11/30) in the venlafaxine XR group, and 32% (11/34) in the placebo group. These percentages decreased to 36% (paroxetine), 32% (venlafaxine XR), and 28% (placebo) when poor responses were imputed for participants with missing HAM-D scores at week 12. The percentages of participants who met response criteria (≥50% reduction in HAM-D score from baseline to week 12) were 68% (23/34) in the paroxetine group, 53% (16/30) in the venlafaxine XR group, and 44% (15/34) in the placebo group. These percentages decreased to 55% (paroxetine), 47% (venlafaxine XR), and 38% (placebo) when poor responses were imputed for participants with missing HAM-D scores at week 12.

Significant beneficial effects of paroxetine and venlafaxine XR relative to placebo were also apparent for the secondary depression outcome variables (MADRS, BDI-II, and GDS; $p \leq 0.01$ for all comparisons; table e-2). Neither treatment had a significant impact on the CAS, but BPRS scores were significantly improved with both paroxetine ($p = 0.01$) and venlafaxine XR ($p = 0.004$) (table e-2) relative to placebo. There were no significant treatment effects on any of the neuropsychological outcome variables. Venlafaxine XR appeared to have a beneficial impact on sleep, as measured by the PSQI ($p = 0.02$, table e-2).

UPDRS total and motor scores improved in all 3 treatment groups, but there were no significant group differences in mean response (table e-2). In particular, there was no evidence of treatment-associated worsening of motor function. Both treatments appeared to favorably impact responses on the bulbar subscale (table e-2), which consists of UPDRS items that evaluate speech, swallowing, salivation, and facial expression.[31]

There was no significant effect of either medication on the PDQ-39 overall score ($p > 0.30$; table e-2). On both the PDQ-39 and the Short Form (SF)–36, however, both medications were associated with improvements on some emotional/mental components of the scales (PDQ-39 Emotional Well-Being subscale; SF-36 Mental Component Summary and Mental Health subscale; table e-2). Paroxetine was also associated with improvements on the Vitality and Role-Emotional subscales of the SF-36 (table e-2). Neither medication was associated with a significant effect on any other PDQ-39 or SF-36 subscale, or on the Schwab and England Activities of Daily Living Scale. Results for the CGI outcomes are presented in the online supplemental material.

**Safety.** One hundred participants (87%) reported at least one adverse event during the trial: 86% in the paroxetine group, 85% in the venlafaxine XR group, and 90% in the placebo group. The most commonly reported AEs (those reported in at least 10% of subjects in at least one treatment group) are listed in table 1. Insomnia was reported significantly less frequently in the paroxetine group than in the venlafaxine XR and placebo groups (table 1).

There were 3 serious adverse events. One subject in the placebo group was hospitalized after 4 days of intermittent chest pressure; however, this subject completed the study. Another subject in the placebo group was hospitalized for a bowel obstruction; this subject also completed the study. One subject in the paroxetine group had frequent, significant ventricular ectopy with >13,000 premature ventricular contractions detected during 24-hour Holter monitoring; the subject withdrew from the trial and treatment assignment was disclosed.

Venlafaxine XR was associated with an increase in sitting blood pressure at the final visit (systolic: 8.5 mm Hg, 97.5% CI 1.2 to 15.9, $p = 0.009$; diastolic: 4.1 mm Hg, 97.5% CI −0.01 to 8.3, $p = 0.03$). Hypertension was reported as an AE in 4 subjects on venlafaxine, 1 subject on paroxetine, and no subjects on placebo (table 1). Paroxetine was associated with an increase in weight (1.3 kg, 97.5% CI −0.1 to 2.7,

**Table 1** Adverse events by treatment group[a]

| Event | Paroxetine (n = 42) | Venlafaxine XR (n = 34) | Placebo (n = 39) |
|---|---|---|---|
| **Sleep** | | | |
| Insomnia[b] | 1 (2.4) | 7 (20.6) | 9 (23.1) |
| Abnormal dreaming | 1 (2.4) | 1 (2.9) | 4 (10.3) |
| Somnolence | 8 (19.1) | 8 (23.5) | 5 (12.8) |
| **Skin** | | | |
| Diaphoresis | 4 (9.5) | 4 (11.8) | 4 (10.3) |
| **Gastrointestinal** | | | |
| Constipation | 6 (14.3) | 7 (20.6) | 5 (12.8) |
| **Reproductive** | | | |
| Sexual dysfunction | 10 (23.8) | 8 (23.5) | 4 (10.3) |
| **Body as a whole** | | | |
| Fatigue | 9 (21.4) | 4 (11.8) | 5 (12.8) |
| **Nervous system** | | | |
| Tremor | 7 (16.7) | 7 (20.6) | 3 (7.7) |
| Dyskinesia | 1 (2.4) | 4 (11.8) | 3 (7.7) |
| Dizziness | 7 (16.7) | 3 (8.8) | 2 (5.1) |
| Headache | 6 (14.3) | 8 (23.5) | 6 (15.4) |
| **Cardiovascular** | | | |
| Hypertension | 1 (2.4) | 4 (11.8) | 0 (0.00) |
| **Urinary** | | | |
| Micturition difficulty | 5 (11.9) | 1 (2.9) | 1 (2.6) |

Abbreviation: XR = extended release.
[a] Values are n (%) of subjects who reported the adverse event at least once during the trial. Adverse events reported in at least 10% of the participants in any treatment group are included.
[b] $p = 0.006$ (paroxetine vs placebo); $p = 0.02$ (paroxetine vs venlafaxine XR).

$p = 0.03$); however, no subjects on paroxetine reported weight gain as an AE, whereas 2 subjects in each of the other 2 groups did. No other significant effects of treatment (relative to placebo) on vital signs were noted.

**Additional outcomes.** For participants assigned to paroxetine, the mean dosage at week 12 was 24 ± 11 mg/day, with 50% of participants taking 30 or 40 mg/day. For the venlafaxine XR group, the mean dosage at week 12 was 121 ± 75 mg/day, with 47% of participants taking 150 or 225 mg/day. For placebo-treated participants, the mean dosage of (placebo) paroxetine at week 12 was 26 ± 12 mg/day and the mean dosage of (placebo) venlafaxine XR at week 12 was 135 ± 76 mg/day. Compliance with study medication, as measured by the percentage of pills apparently taken out of those expected to be taken, averaged 94%–97% for paroxetine/placebo and 94%–96% for venlafaxine XR/placebo. Finally, guesses of treatment assignments did not suggest any significant compromise of the blind (details available in the online supplemental material).

**DISCUSSION** This is the largest randomized, placebo-controlled clinical trial of commonly used antidepressant medications for the treatment of dPD, had the longest observation period, and was the first to evaluate an SNRI. The study demonstrated that both paroxetine (an SSRI) and venlafaxine XR (an SNRI) are more effective than placebo for the treatment of depressive symptoms. This finding was consistent across all measures of dPD that were used.

Our findings differ somewhat from those of the trial by Menza et al.[5] In that single-site trial, 52 patients with dPD were randomized to receive paroxetine (n = 18), nortriptyline (a TCA, n = 17), or placebo (n = 17) for 8 weeks. Nortriptyline, but not paroxetine, was found to be significantly better than placebo in decreasing the mean score on the HAM-D. This finding led some to question the use of SSRIs in dPD and whether TCAs should be the preferred treatment of dPD.[33] There are several possible explanations for the different results, including shorter duration of treatment, higher dropout rate, and strategy used for missing data in the study by Menza et al. (see online supplemental material for further discussion).

In our study we observed a fairly prominent improvement in mean HAM-D score in the placebo group (figure 2), which was consistent across all of our measures of depression and has been demonstrated in other antidepressant treatment studies.[34] Despite this response, and a sample size smaller than anticipated, we were still able to detect significant beneficial effects of paroxetine and venlafaxine XR using 4 different depression rating scales. Although the observed percentages of participants in each treatment group who achieved a ≥50% reduction in HAM-D score supported the results of the primary analysis, these treatment group comparisons were not statistically significant. It is well known that there can be a substantial loss of information when continuous outcome variables are dichotomized[35]; this, coupled with our substantially reduced sample size, is a possible explanation for the lack of statistical significance of treatment effects on this outcome. Although the effects of paroxetine and venlafaxine XR appeared to be quite comparable, our sample size was not large enough to make any conclusions concerning the equivalence of these effects.

Other approaches toward the treatment of depression in PD have been to consider the effects of antiparkinsonian medications on mood. A recent study reported results from a randomized, double-blind, placebo-controlled trial of the dopamine agonist pramipexole, which was thought to have antidepressant effects, involving 296 participants

with dPD who were followed for 12 weeks.[36] The effect of pramipexole, while statistically significant, was considerably smaller (1.9 points on the BDI, version 1A) than the effects of paroxetine and venlafaxine XR observed in our trial (4.4–4.5 points in the BDI-II).

This study demonstrates the efficacy and safety of antidepressants in patients with dPD without dementia. Both study medications were significantly more effective than placebo on a number of depression scales and did not show any significant side effects or worsening of PD motor function. Emotional subscale scores, but not overall QOL, improved with both medications.

As with other depression treatment studies, we found that some subjects failed to respond to the study medications while others improved but did not achieve full remission. Our sample size was not large enough to identify subject characteristics that predict response to study medications. Further research aimed at understanding predictors of response, including identification of patients who may respond preferentially to one class of medication vs another, is warranted.

## AUTHOR CONTRIBUTIONS

Dr. Richard: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision, obtaining funding. Dr. McDermott: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, statistical analysis. Dr. Kurlan: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Dr. Lyness: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Como: drafting/revising the manuscript, study concept or design, study supervision. N. Pearson: analysis or interpretation of data, acquisition of data, study supervision. S.A. Factor: drafting/revising the manuscript, acquisition of data, study supervision. Dr. Juncos: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Dr. Serrano Ramos: drafting/revising the manuscript, acquisition of data. Dr. Brodsky: drafting/revising the manuscript, acquisition of data. Dr. Manning: drafting/revising the manuscript, study concept or design, acquisition of data. Dr. Marsh: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Dr. Shulman: drafting/revising the manuscript, acquisition of data. Dr. Fernandez: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, study supervision. Dr. Black: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Panisset: drafting/revising the manuscript, acquisition of data. Dr. Christine: drafting/revising the manuscript, acquisition of data. Dr. Jiang: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, study supervision. Dr. Singer: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Horn: drafting/revising the manuscript, acquisition of data, study supervision. Dr. Pfeiffer: drafting/revising the manuscript, acquisition of data. Dr. Rottenberg: drafting/revising the manuscript, acquisition of data. Dr. Slevin: drafting/revising the manuscript, acquisition of data. Dr. Elmer: drafting/revising the manuscript, acquisition of data. Dr. Press: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Hyson: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. McDonald: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision, obtaining funding.

## DISCLOSURE

Dr. Richard serves on a scientific advisory board for the Michael J. Fox Foundation; has received a speaker honorarium from Teva Pharmaceutical Industries Ltd.; and receives/has received research support from Neurologix, Inc., Eli Lilly and Company, the NIH/NINDS, Cornell University, and the Michael J. Fox Foundation. Dr. McDermott serves on data safety monitoring boards for Isis Pharmaceuticals, Inc., Biogen Idec, the ALS Association/FDA, and the Muscular Dystrophy Association; serves on the editorial board of *Movement Disorders*; has served as a consultant for the New York State Department of Health, Teva Pharmaceutical Industries, Ltd., Synosia, Inc., Smith and Nephew, Inc., and IMPAX Laboratories, Inc.; and receives/has received research support from Forest Laboratories, Inc., Medivation, Inc., NeuroSearch, Boehringer Ingelheim, Pfizer Inc, Endo Pharmaceuticals, the NIH, the CDC, the FDA, the Michael J. Fox Foundation, Spinal Muscular Atrophy Foundation, Muscular Dystrophy Association, and American Dental Association. Dr. Kurlan serves as Supplement Editor for *Neurology*® and receives research support from Boehringer Ingelheim, Kyowa Hakko Kirin Pharma, Inc., Neurologix, Inc., and the NIH. Dr. Lyness serves on data safety monitoring board for the NIH/NIA; serves as Consulting Editor for *Psychology and Aging*; and receives/has received research support from the NIH (NIMH, NIA, NINDS). Dr. Como and N. Pearson report no disclosures. Dr. Factor serves as a Section Editor for *Current Treatment Options in Neurology* and *Clinical Neurology and Neuroscience*; receives publishing royalties for *Parkinson's Disease Diagnosis and Clinical Management* (Demos, 2008) and *Drug Induced Movement Disorders* (Blackwell Futura, 2005); receives research support from Teva Pharmaceutical Industries Ltd., Ipsen, Merck Serono, Ceregene, the NIH (NHLBI, NINDS), and the Michael J. Fox Foundation; and has served as an expert witness in a medico-legal proceeding. Dr. Juncos has served on the speakers' bureaus of UCB and Novartis and receives research support from the NIH (NINDS, NICHD). Dr. Serrano Ramos has received research support from the NIH. Dr. Brodsky has served on scientific advisory boards for Ipsen, Merz Pharmaceuticals, LLC, and Teva Pharmaceutical Industries Ltd.; has received speaker honoraria from Teva Pharmaceutical Industries Ltd. and Medtronic, Inc.; and serves on speakers' bureaus for Teva Pharmaceutical Industries Ltd., Allergan, Inc., Merz Pharmaceuticals, LLC, and Ipsen. Dr. Manning reports no disclosures. Dr. Marsh serves on scientific advisory boards for Merck Serono, Ovation Pharmaceuticals (Lundbeck Inc.), ACADIA Pharmaceuticals, Boehringer Ingelheim, National Parkinson Foundation, American Parkinson's Disease Association, and Parkinson Study Group; serves on the editorial board of the *Journal of Parkinson's Disease*; receives publishing royalties for *Psychiatric Issues in Parkinson's Disease: A Practical Guide* (Taylor & Francis/ Informa, 2005); serves as a consultant for Merck Serono, Ovation Pharmaceutical (Lundbeck Inc.), ACADIA Pharmaceuticals, and Boehringer Ingelheim; and receives/has received research support from Forest Laboratories, Inc., Eli Lilly and Company, Boehringer Ingelheim, the NIH, the American Psychiatric Association, Baylor College of Medicine, and the Michael J. Fox Foundation. Dr. Shulman serves as Editor-in-Chief of the *Neurology Now* Patient Book Series and on the editorial advisory board of *Neurology Now*; receives publishing royalties for *Parkinson's Disease: A Complete Guide for Patients and Families* (Johns Hopkins University Press, 2000, 2007); receives research support from Teva Pharmaceutical Industries Ltd., the NIH, and the Michael J. Fox Foundation; and has served as a consultant in medico-legal proceedings. Dr. Fernandez serves on scientific advisory boards for Solvay Pharmaceuticals, Inc. and EMD Serono, Inc.; has received funding for travel or speaker honoraria from Medical Communications Media, Health Professions Conferencing, Ipsen, Merz Pharmaceuticals, LLC, and US World Meds; serves as Medical Editor of the Movement Disorders Society's Web site; is patent co-owner of COMPRESS, a neurosurgical candidate selection tool; receives publishing royalties from Demos, Manson, and Springer; and receives/has received research support from Abbott, ACADIA Pharmaceuticals, Biotie Therapeutics, EMD Serono, Inc., Novartis, Teva Pharmaceutical Industries Ltd., the NIH/NINDS, Huntington Study Group, Movement Disorders Society, Parkinson Study Group, the Michael J. Fox Foundation, National Parkinson Foundation, and Society of Progressive Supranuclear Palsy. Dr. Black serves on a scientific advisory board for the Tourette Syndrome Association; serves on the editorial advisory board of *The Open*

*Neuroimaging Journal*; is listed as author on patents re: Novel methods for medicinal dosage determination and diagnosis and A2A antagonists as cognition and motor function enhancers; has served as a consultant for Synosia Therapeutics, Merck Serono, and Gerson Lehman Group; and receives/has received research support from Synosia Therapeutics, ACADIA Pharmaceuticals, the NIH (NIDDK, NIMH, NCRR), the Tourette Syndrome Association, and the McDonnell Center for Systems Neuroscience at Washington University. Dr. Panisset serves on scientific advisory boards for Teva Pharmaceutical Industries Ltd., Novartis, Allergan, Inc., and Merz Pharmaceuticals, LLC; has received funding for travel or speaker honoraria from Merz Pharmaceuticals, LLC, Medtronic, Inc., and Teva Pharmaceutical Industries Ltd.; and receives research support from Allon Therapeutics, Inc. and Teva Pharmaceutical Industries Ltd. Dr. Christine receives research/salary support from Genzyme Corporation, Kyowa Hakko Kirin Pharma, Inc., Eisai Inc., and the NIH/NINDS. Dr. Jiang reports no disclosures. Dr. Singer serves on scientific advisory boards for Lundbeck Inc., Merz Pharmaceuticals, LLC, and Ipsen; has received funding for travel from Ipsen; and receives/has received research support from Schwartz Biomedical, LLC, Merz Pharmaceuticals, LLC, Teva Pharmaceutical Industries Ltd., the NIH, Parkinson Study Group, Huntington Study Group, and National Parkinson Foundation. Dr. Horn reports no disclosures. Dr. Pfeiffer serves on the scientific advisory board for the National Parkinson Foundation; serves as Co-Editor in Chief of *Parkinsonism and Related Disorders* and on the editorial board of the *Journal of Parkinson's Disease*; receives publishing royalties for *Parkinson's Disease* (Taylor & Francis, 2008-present), *Parkinson's Disease and Nonmotor Dysfunction* (Humana, 2008–present), and *Neuro-Gastroenterology* (Butterworth-Heinemann, 2008); serves as a consultant for Solvay Pharmaceuticals, Inc., Theravance Inc., Genactis, Schlesinger Associates, and UCB; serves on speakers' bureaus for Boehringer Ingelheim, Novartis, and Teva Pharmaceutical Industries Ltd.; receives research support from Novartis, Boehringer Ingelheim, UCB/SCHWARZ PHARMA, Santhera Pharmaceuticals, Molecular Biometrics, Columbia University, Weill Cornell Medical College, Northwestern University, Indiana University, Parkinson Study Group, and the Michael J. Fox Foundation; and has served as a consultant in medico-legal proceedings. Dr. Rottenberg reports no disclosures. Dr. Slevin serves/has served on speakers' bureau for Boehringer Ingelheim, Novartis, and Teva Pharmaceutical Industries Ltd.; and receives/has received research support from Solvay Pharmaceuticals, Inc. and the NIH. Dr. Elmer has received research support from Teva Pharmaceutical Industries Ltd. and serves on speakers' bureaus for Teva Pharmaceutical Industries Ltd., GlaxoSmithKline, Novartis, and UCB. Dr. Press receives/has received research support from the NIH (NIMH, NIA), the Milton Fund, and the Harvard Center for Neurodegeneration and Repair. Dr. Hyson has served on scientific advisory boards for Biogen Idec; and has received speaker honoraria from Merz Pharmaceuticals, LLC and Biogen Idec. Dr. McDonald serves as Triage Editor for *American Journal of Geriatric Psychiatry* and on the editorial board of the *Journal of ECT*; serves as a consultant for Cervel Neurotech; and receives/has received research support from the NIH/NIMH, GlaxoSmithKline, Wyeth, Boehringer Ingelheim, and Janssen.

*Received June 8, 2011. Accepted in final form October 18, 2011.*

## REFERENCES


1. Liu C-Y, Wang S-J, Fuh J-L, Lin C-H, Yang Y-Y, Liu H-C. The correlation of depression with functional activity in Parkinson's disease. J Neurol 1997;244:493–498.
2. Kuopio A, Marttila R, Hellenius H, Toivonen M, Rinne U. The quality of life in Parkinson's disease. Mov Disord 2000;15:216–223.
3. Phillips P. Keeping depression at bay helps patients with Parkinson's disease. JAMA 1999;282:1118–1119.
4. The Global Parkinson's Disease Survey (GPDS) Steering Committee. Factors impacting on quality of life in Parkinson's disease: results from an international survey. Mov Disord 2001;17:60–67.
5. Menza M, Dobkin RD, Marin H, et al. A controlled trial of antidepressants in patients with Parkinson disease and depression. Neurology 2009;72:886–892.
6. Devos D, Dujardin K, Poirot I, et al. Comparison of desipramine and citalopram treatments for depression in Parkinson's disease: a double-blind, randomized, placebo-controlled study. Mov Disord 2008;23:850–857.
7. Yeragani VK, Roose S, Mallavarapu M, Radhakrishna RK, Pesce V. Major depression with ischemic heart disease: effects of paroxetine and nortriptyline on measures of nonlinearity and chaos of heart rate. Neuropsychobiology 2002;46:125–135.
8. Yeragani VK, Pesce V, Jayaraman A, Roose S. Major depression with ischemic heart disease: effects of paroxetine and nortriptyline on long-term heart rate variability measures. Biol Psychiatry 2002;52:418–429.
9. Nelson J, Kennedy J, Pollock B, et al. Treatment of major depression with nortriptyline and paroxetine in patients with ischemic heart disease. Am J Psychiatry 1999;156:1024–1028.
10. Salzman C. Pharmacologic treatment of depression in the elderly. J Clin Psychiatry 1993;54:23–28.
11. Altamura AC, DeNovelis F, Guercetti G. Fluoxetine compared with amitriptyline in elderly depression: a controlled clinical trial. Int J Clin Pharmacol Res 1989;9:391–396.
12. Feighner J, Boyer W, Meredith C. An overview of fluoxetine in geriatric depression. Br J Psychiatry 1988;153:105–108.
13. Cohn C, Shrivastava R, Mendels J. Double-blind, multicenter comparison of sertraline and amitriptyline in elderly depressed patients. J Clin Psychiatry 1990;5:28–33.
14. Dunner D, Cohn J, Walshe TI. Two combined, multicenter double-blind studies of paroxetine and doxepin in geriatric patients with major depression. J Clin Psychiatry 1992;53:57–60.
15. Guillibert E, Pelicier Y, Archambault J, Chabannes J, Clerc G, Desvilles M. A double-blind, multicentre study of paroxetine versus clomipramine in depressed elderly patients. Acta Psychiatr Scand 1989;80:132–134.
16. Simons J. Fluoxetine in Parkinson's disease. Mov Disord 1996;11:581–582.
17. Jansen Steur H. Increase of Parkinson disability after fluoxetine medication. Neurology 1993;43:211–213.
18. Jimenez-Jimenez F, Tejeiro J, Martinez-Junquera, et al. Parkinsonism exacerbated by paroxetine. Neurology 1994;44:2406.
19. Dubovsky S. Geriatric neuropsychopharmacology. In: Coffey C, Cummings J, eds. Textbook of Geriatric Neuropsychiatry. Washington, DC: American Psychiatric Press; 1994: 595–631.
20. Hirschfeld R. Efficacy of SSRIs and newer antidepressants in severe depression: comparison with TCAs. J Clin Psychiatry 1999;60:326–335.
21. Entsuah A, Huang H, Thase M. Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine's elective serotonin reuptake inhibitors, or placebo. J Clin Psychiatry 2001;62:869–877.
22. Benedictis E. Double-blind comparison of venlafaxine and amitriptyline in outpatients with major depression with or without melancholia. J Psychopharmacol 2000;14:61–66.
23. Applebaum PS, Grisso T. MacCAT-CR: MacArthur Competence Assessment Tool for Clinical Research. Sarasota, FL: Professional Resource Press; 2001.

24. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. Washington, DC: American Psychiatric Association; 1994.
25. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.
26. Montgomery S, Åsberg M. New depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382.
27. Beck AT, Steer RAB, R., Ranieri W. Comparison of Beck Depression Inventories IA and II in psychiatric outpatients. J Pers Assess 1996;67:588–597.
28. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatry Res 1983;17:37–49.
29. Conners C, Barkley R. Rating scales and checklists for psychopharmacologic trials. Psychopharmacol Bull 1985;21:809–854.
30. Fahn S, Elton RL. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent Developments in Parkinson's Disease. Florham Park, NJ: MacMillan Healthcare Information; 1992:153–163.
31. Uc EY, McDermott MP, Marder KS, et al. Incidence of and risk factors for cognitive impairment in an early Parkinson disease clinical trial cohort. Neurology 2009;73:1469–1477.
32. Little RJA, Rubin DB. Statistical Analysis with Missing Data, Second Edition. Hoboken: John Wiley and Sons; 2002.
33. Okun MS, Fernandez HH. Will tricyclic antidepressants make a comeback for depressed Parkinson disease patients. Neurology 2009;72:868–869.
34. Brunoni AR, Lopes M, Kaptchuk TJ, Fregni F. Placebo response of non-pharmacological and pharmacological trials in major depression: a systematic review and meta-analysis. PLoS One 2009;4.
35. Senn S, Julious S. Measurements in clinical trials: a neglected issue for statisticians? Stat Med 2009;28:3189–3209.
36. Barone P, Poewe WA, S., Debieuvre C, et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2010;9:573–580.